II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-25, 32-43, and 68-77 were pending prior to the Office Action dated January 10, 2006. Claims 3, 9, 15-16, and 36-37 have been amended and claim 24 has been cancelled. Claim 78 has been added based on the elements recited in claim 79. No new matter has been added.

B. Claims 1-4, 7-25, 32-43, and 68-77 Are Enabled

The Action rejects claims 1-4, 7-25, 32-43, and 68-77 under 35 U.S.C. § 112, first paragraph, because the specification is alleged as not reasonably providing enablement for distal or systemic administration of an adenoviral vector expressing any fragment of MDA-7 polypeptides for treating an angiogenesis-dependent tumor. It admits the specification is enabling for intratumoral injection of a nucleic acid expressing full-length or secreted MDA-7. Action at page 4. This Action also indicates that the reasoning previously provided for this rejection in prior Actions still applied. Applicants respectfully traverse this rejection.

1. Routes of Administration

This Action and previous Actions raised several issues regarding routes of administration that indicate undue experimentation would be required to practice the invention. These related to gene therapy and viral vectors. Applicants respectfully traverse this ground of the rejection.

a) Gene Therapy

The Action contends that the gene therapy practitioner recognized that gene therapy for angiogenesis and cancer was neither accepted nor routine and that such a person awaited significant development and guidance for its practice. The Action relies on the references of Deonarain, Miller, Makrides *et al.* ("Makrides"), and Boucher *et al.* ("Boucher") for its position that gene targeting to desired cells and tissue has yet to become routine in the art. Deonarain is said to illustrate this point.

Moreover, the Action contends that Miller illustrates that no single vector is considered to be universally appropriate. Miller is alleged to teach that because of the underdeveloped state of vector targeting, that gene therapy, as represented by the cystic fibrosis treatment, has relied largely on localized delivery.

Furthermore, the Makrides reference was cited to provide further evidence that there is an association between the vector system chosen and the production of a therapeutic protein, which is relevant to therapeutic efficacy. The Boucher reference is cited as indicating that another element critical to the success of gene delivery is the host resistance to foreign gene transfer. It is said to be relevant because it says that host cells have an innate ability to defend themselves against the penetration of gene therapy vectors.

Overall, the previous Final Action concluded that the claims are not enabled for their full scope to the extent they cover *in vivo* applications by any means of delivery, particularly from a distal site.

Once again, a closer examination of the cited references reveals that they do not support the Action's conclusions and also, there is evidence that indicates gene therapy can be practiced according to the specification and knowledge of the skilled artisan.

The Action cites the reference of Miller as saying, "No single delivery system is likely to be universally appropriate, for instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer." Action dated 6/15/04 at page 8, citing page 190 of Miller. By its own admission, the Action renders the next citation to Miller and the citation to Boucher irrelevant because they both involve statements relating to the treatment of cystic fibrosis, while the present invention is related to inhibiting angiogenesis.

As for the reliance on the reference of Makrides, this reference merely states that "the choice of an expression system for production of recombinant proteins depends on many factors...." However, it is not clear how this statement indicates that undue experimentation would be required to practice the invention. Moreover, this reference says nothing about the ability to express MDA-7 or any limitations there might be with its expression.

In fact, there is evidence to support the contention that the claims are enabled. In addition to the data regarding a therapeutic effect from administration of Ad-mda7 in the specification (Examples 1, 4, 6, 9, 10 and 11), there is information relating to the administration of an MDA-7-encoding plasmid in a DOTAP:cholesterol liposome to a nude mouse. In the Declaration of Sunil Chada ("2003 Chada Declaration"), Dr. Chada sets forth that nude mice with tumors exhibited reduced tumor growth and reduced levels of CD31 staining after treatment with the DOTAP:Chol-*mda-7* complex. Declaration at ¶ 9. A reduction in levels of CD31 staining is indicative of reduced vascularization, *i.e.,* inhibition of angiogenesis.

The Action does not address the evidence previously provided by Applicants, which is provided again with this response. In the 2003 Chada Declaration, evidence is provided that a plasmid encoding MDA-7 achieves an anti-angiogenic effect *in vivo*.

Additionally, other evidence indicates the invention will work even if the MDA-7 is not administered intratumorally. In a published patent application with some of the same inventors, there is additional data regarding MDA-7 and angiogenesis. In WO 04/078124, it states in Example 7:

> Studies were conducted to determine whether sMDA-7 produced by 293-mda-7 cells can systemically inhibit tumor growth. Mice were inoculated subcutaneously with A549 tumor cells in the lower right flank. When the tumors reached 50-100 mm^3, 293 cells producing sMDA-7 protein (293-mda-7 cells) or parental 293 cells (control) were encapsulated in Matrigel and implanted subcutaneously in the upper right flank. Tumor measurement was initiated after

implantation of 293 cells. The growth of A549 lung tumor xenografts was significantly less ($P = 0.001$) in the mice treated with 293-mda-7 cells than in the control group (FIG. 6D). Compared with tumor growth in the control mice, the growth of the tumors in mice implanted with the encapsulated 293-mda-7 cells was suppressed by 40-50%. To confirm that the inhibitory effect was due to sMDA-7, serum samples from animals were tested for MDA-7 protein by western blot analysis and ELISA. Intense banding of sMDA-7 at the expected 40-kDa size was observed in the serum of animals implanted with 293-mda-7 cells by western blot analysis. However, faint bands were also observed in the serum of control animals, indicating some cross-reactivity with mouse serum proteins. The serum levels of circulating sMDA-7 detected by ELISA 3 days postimplantation was approximately 50 ng/ml.

At the end of the experiment, tumors and injected Matrigel containing 293-mda-7 cells were harvested and evaluated. Gross examination of the tumors indicated that the tumor growth in animals that received 293-mda-7 cells was inhibited. Histopathologic analysis of the tumor tissues demonstrated no differences between the specimens from animals receiving 293 cells and those from animals receiving 293-mda-7 cells. Additionally, the tumors from mice treated with 293-mda-7 were significantly ($P = 0.001$) less vascular than were the tumors from mice treated with parental 293 cells, as evidenced by CD31-positive staining (FIG. 6E). Immunohistochemical analysis of the Matrigel from animals receiving 293-mda-7 cells demonstrated MDA-7 protein expression. In contrast, MDA-7 was not detected in the Matrigel recovered from animals receiving parental 293 cells. These results demonstrate that **sMDA-7 systemically** inhibited tumor growth **by inhibiting angiogenesis**.

WO 04/078124 at page 122 (emphasis added). This text indicates that subcutaneous administration of MDA-7 in the upper flank—as opposed to the lower flank where the tumor was—achieved systemic inhibition of angiogenesis. Post-filing date successes following the *teachings* of the application at issue are probative to show enablement of the claimed invention. *See Gould v. Quigg,* 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987) (stating that a later dated publication ... [may be] offered ... as evidence that the disclosed device would have been operative). This additional evidence indicates the claimed invention is enabled beyond just intratumoral injection.

b) Viral Vectors

The Action contends that adenovirus tissue tropism in respiratory epithelium cells offers additional evidence that targeting of adenovirus may be required for gene therapy. It states that the reference of Miller teaches that adenoviral diseases are usually associated with respiratory epithelium. It contends that the issue of tissue tropism has been raised because if viral vectors are administered systemically from a site distal from a tumor, it may require a targeting mechanism so that a sufficient amount of the vector can be localized to the site of the targeted tumor.

Applicants note that this is arguably relevant to only one particular embodiment of the claimed invention: systemic delivery of an adenovirus vector to non-lung tissue. The specification indicates that different routes of administration are contemplated depending on the location and nature of the lesion. Specification at page 54, lines 25-30. The specification indicates that for treatment of a tumor, administration intratumorally is specifically contemplated but that continuation administration may be applied when appropriate, for example, to a tumor bed. Specification at pages 55-56. This shows two things. First, the specification teaches a situation in which systemic administration can be accomplished without tissue tropism being an issue. Second, it shows that the skilled artisan was aware that different situations call for different considerations in terms of mode of administration and construct used.

Moreover, Applicants address the issue of whether adenovirus can infect other tissues. The specification of the instant application shows that adenovirus infected breast cancer cells (Example 4), in addition to lung cancer cells (Example 10). Moreover, numerous publications and patent applications have shown that adenovirus[1] can be used to treat a multitude of different cancers and infect a wide variety of tissues in animals and patients; these include, for example,

[1] Applicants cite publications involving Advexin®, an adenovirus product carrying the p53 gene, which is owned by Introgen Therapeutics, Inc., the licensee of the present application.

bladder (Pagliaro *et al.*), breast (WO 04/078124 page 190-191), glioma (Lang *et al.*), head and neck (Clayman *et al.*), prostate (Pisters *et al.*), and ovarian (Wolf *et al.*).

Applicants submit that the tropism issue raised in the Action does not render the claimed invention not enabled. Consequently, they respectfully request this rejection be withdrawn.

C. Claims 75 and 76 Are Definite

The Action rejects claims 75 and 76 as indefinite because it contends that claims 75 and 76 use the term "viral particles" and that this term lacks antecedent basis in claim 8, which recites "viral vector." It cites a Google definition as evidence. Applicants respectfully traverse this rejection.

"The mere fact that a term or phrase used in the claim has no antecedent basis in the specification disclosure does not mean, necessarily, that the term or phrase is indefinite. There is no requirement that the words in the claim must match those used in the specification disclosure. Applicants are given a great deal of latitude in how they choose to define their invention so long as the terms and phrases used define the invention with a reasonable degree of clarity and precision." MPEP 2173.05(e); *see also* MPEP 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)).

In this case, the skilled artisan would understand that the number of viral particles referred to in claims 75 and 76 refers to the amount of viral vector. The specification confirms this. It states, "In certain embodiments, the nucleic acid is a viral vector, wherein the viral vector dose is or is at least 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13} or higher pfu or viral particles." Specification at page 9, lines 15-17. Moreover, the "Google" definitions cited in the Action do not contradict this understanding. The term "viral vector" is said to mean "a type of virus used in cancer therapy." The term "viral particles" refers to "the new viruses reproduced inside a cell." Both terms refer to viruses. There is no basis for saying a viral vector and a viral

particle are "structurally different substances" as asserted on page 6 of the Action. In addition, there is no reason a skilled person would not understand the scope of claims 75 and 76.

Furthermore, Applicants note that the MPEP indicates that "Examiner should suggest corrections to antecedent problems" under § 2173.05(e). In this case, no suggestions have been made; it is believed this is the case because the claims are wholly consistent with the usage of such terms in the gene therapy area and that any suggestion would *create* rather than eliminate uncertainty regarding the meaning of the claims.

Accordingly, Applicants respectfully request this rejection be withdrawn.

D. Claims 1-4, 7, 8, 10-15, 24, 25, 32-36, 42, 43, 68-74, and 77 Are Not Anticipated

The Action rejects claims 1-4, 7, 8, 10-15, 24, 25, 32-36, 42, 43, 68-74, and 77 under 35 U.S.C. § 102(e) as anticipated by Fisher *et al.* (U.S. Patent 6,355,622) ("Fisher"), as evidenced by Folkman *et al.*, *Nature*, 339:58-61, 1989 and *J. Biol. Chem.*, 267:10931, 1992 ("Folkman references"). Fisher is said to teach a method of inhibiting cancer in a subject comprising intratumoral administration to nude mice bearing cervical carcinoma cells replication deficient adenoviral vector encoding full-length mda-7 protein. The Action admits that Fisher does not literally teach that a tumor is an angiogenesis-related disease. It argues that it was well known in the art that tumors belong to the class of angiogenesis-related diseases and that angiogenesis accompanies tumor growth and metastasis as evidenced by the Folkman references. The Action concludes that Fisher meets every limitation of the elected species, and thus, anticipates the claimed invention. Applicants respectfully traverse this rejection.

The Federal Circuit case of *Kalman v. Kimberly-Clark Corp.,* 713 F.2d 760 (Fed. Cir. 1983) states that *identity of invention* is required for anticipation. *Each element* of the claim in issue must be found in a single prior art reference. The claims recite:

> A method of inhibiting angiogenesis in a human patient in need of such treatment comprising administering to the patient an effective amount of a human melanoma differentiation antigen-7 (MDA-7) polypeptide or a nucleic acid expressing the human MDA-7 polypeptide in eukaryotic cells to inhibit angiogenesis.

The Fisher patent, however, does not even mention angiogenesis or inhibition of angiogenesis. In fact, the Action concedes this. Action at page 7. However, the Action argues that because the Folkman references teach that cancer is angiogenesis-related disease, they are evidence that Fisher teaches every element of the claimed invention. This argument is not valid.

Just because a tumor is an angiogenesis-disease does not mean that every agent that treat tumors is going to treat an angiogenesis-related disease, or more specifically, that it will inhibit angiogenesis. This is the argument the Action essentially employs. The fact is that MDA-7 was believed to work because it induced apoptosis, not because it inhibited angiogenesis, particularly not to the level of inhibition demonstrated by MDA-7. There was no evidence at the time the above-referenced application was filed that taught or suggested that MDA-7 could also inhibit angiogenesis, which works by a different mechanism than the ability to induce apoptosis. Therefore, there is no implicit understanding by the skilled artisan that Fisher teaches a method of inhibiting angiogenesis.

Furthermore, Fisher does not "intrinsically" or inherently anticipate the claimed invention. The Action contends that "as long as Fisher's method suppressed tumor growth, it intrinsically also suppressed tumor angiogenesis." Action at page 11. However, anticipation requires that ***every*** element be taught and Fisher did not intrinsically teach inhibiting angiogenesis *in a human patient* because even if the treatment of Fisher resulted in suppression of tumor growth, this treatment was effected in *mice*, <u>not</u> humans. Fisher never performed the method in humans and, and therefore, Fisher does not inherently or "intrinsically" anticipate the

claimed invention. Fisher does not teach inhibiting angiogenesis because this method was invented by the present inventors, not by Fisher *et al.* Applicants respectfully request this rejection be withdrawn.

Applicants note that certain claims have not been rejected as anticipated by Fisher. Claims 9, 16-23, 37-41, 75, and 76 were not rejected as anticipated by Fisher and any argument that Fisher "intrinsically" teaches an element does not apply to these claims whether to support an anticipation or obviousness rejection. This is equally true of new claim 78, which recites a number of cancers, none of which are disclosed in Fisher.

Furthermore, the claimed invention was not obvious in view of Fisher because the results were surprising and unexpected. Fisher discloses ways in which MDA-7 may work to achieve tumor growth suppression:

> In many cancer cells, including breast carcinoma (MCF-7 and T47D), glioblastoma (GBM-18 and T98G) and melanoma (H0-1 and C8161), infection with Ad.mda-7 S resulted in the induction of programmed cell death (apoptosis). This effect was not elicited in normal cells even after infection with high multiplicities of infection (100 pfu/cell) with Ad.mda-7 S. In other cancer cell types, growth suppression (as indicated by a suppression in colony formation in monolayer culture) was apparent without signs of apoptosis, as indicated by nuclear morphology changes, formation of nucleosomal ladders or a positive TUNEL reaction. These results indicate that the Ad.mda-7 S virus can selectively inhibit the growth of human cancer cells in vitro. Moreover, in specific cancer cell types growth suppression correlates with induction of apoptosis. These observations suggest that inhibition in cancer growth induced by mda-7 can occur by multiple pathways.

Fisher patent, 3rd to last paragraph in specification. Significantly, no mention is made of angiogenesis. Moreover, the functions identified involved apoptosis or other growth changes on the actual cancer cell itself. At best, Fisher indicates that MDA-7 can achieve growth suppression by acting only on the tumor or cancer cell. In no way does Fisher indicate or suggest that MDA-7 may act on a tumor by affecting the blood vessels feeding the tumor or on any cells that are not part of the tumor.

Other references that had been published prior to the filing date of the present application are also focused on apoptosis. In a paper authored by some of the Fisher inventors, the title is "The cancer growth suppressor gene *mda-7* selectively induces apoptosis in human breast cancer cells and inhibits tumor growth in nude mice." Su *et al., Proc. Natl. Acad. Sci. USA*, 95:14400-14405, 1998. In this paper, the authors describe how MDA-7 was identified as involved in the terminal differentiation of melanoma cells (page 14400, right-hand column) and report that they used DNA extraction, fragmentation assays, and TUNEL assays to evaluate MDA-7's ability to induce apoptosis in cancer cells (page 14401-14404). Furthermore, in this paper only cancer cells were exposed *in vivo* to MDA-7 as these cancer cells were injected with an Ad-mda7 expression construct before they were placed in a mouse animal model.

The focus on MDA-7 as only an apoptosis inducer is in distinct contrast to the instant application, which is why it was surprising and unexpected that MDA-7 could inhibit angiogenesis. The present specification provides specific data that the process of angiogenesis is specifically inhibited. On page 92 at lines 15-20 the specification indicates that tumors treated *in vivo* with Ad-mda7 had fewer blood vessels than untreated tumors. Furthermore, on page 99, data is provided that tumors treated with Ad-mda7 had significantly lower levels of CD31 expression, which indicates fewer blood vessels. The application also showed that MDA-7 inhibited endothelial cell differentiation *in vitro* (page 98) and inhibited tube formation (page 100). The evidence in the application further provide evidence of the surprising and unexpected results that MDA-7 could be as effective at inhibiting angiogenesis as it was. As little 0.5-1.0 ng/ml of MDA-7 protein inhibited tube formation (page 100 and FIG. 22).

Additionally, the results in the present specification were surprising and unexpected because they showed that the human MDA-7 protein would work on *mouse* cells. The *in vivo*

experiment involved human cancer cells transplanted into a mouse, but the fact that fewer blood vessels were observed indicates that *mouse* cells involved in angiogenesis were responding to the *human* protein. Specification at page 99. None of the data previously involving MDA-7 in the cited references concerned effects of human MDA-7 on cells other than human cells. *See* Fisher and Su *et al.*

Moreover, the human and mouse proteins are only 68.6% identical (*see* sequence alignment). The Patent Office readily cites a number of papers as evidence that even single amino acid changes can alter the function of a protein. *See e.g.*, Witkowski *et al.* and Seffernick *et al.*.

Therefore, for several reasons the data and invention in the present application were surprising and unexpected. Consequently, Applicants contend that Fisher neither anticipates or renders obvious the claimed invention. Accordingly, Applicants respectfully request this rejection be withdrawn.

E. Claims 1-4, 7-25, 35-43, and 68-77 Are Provisionally Rejected

The Action provisionally rejects claims 1-4, 7-25, 35-43, and 68-77 under 35 U.S.C. § 102(e) over copending Application No. 09/615,154. It states that if this application were to publish under 35 U.S.C. § 122(b) or be patented, the rejection would no longer be provisional.

Because the rejection is provisional, Applicants need not address this rejection at this time.

F. Claims 1-4, 7-25, 35-43, and 68-77 Are Not Derived from a Co-Pending Application

The Action rejects claims 1-4, 7-25, 35-43, and 68-77 under 35 U.S.C. § 102(f) over copending Application No. 09/615,154. The Action argues that because the elected invention is drawn to treating an angiogenesis-related tumor in a patient, the instant claims are obvious

variants of the claims in the co-pending application. Application respectfully traverse this rejection.

There is no basis for asserting that a method of inhibiting angiogenesis is obvious from a method of treating a tumor. As discussed above, not every method of treating a tumor can be used as a method if inhibiting angiogenesis. The claimed method is to a method of inhibiting angiogenesis. The particular species elected is a method of inhibiting angiogenesis in a patient with an angiogenesis-related disease that is an angiogenesis-related cancer. The Action ignores that the invention is a method for inhibiting angiogenesis.

Even if tumors are angiogenesis-dependent, Applicants have argued above that there is no basis for contending that all cancer treatments inhibit angiogenesis. Moreover, there is no basis for saying why it would be obvious to use a cancer treatment to inhibit angiogenesis, especially where the cancer treatment is MDA-7. MDA-7 had been described only in the context of terminal differentiation and apoptosis prior to the present specification. The present rejection is defective because it identifies no evidence as to why the skilled artisan would consider the claimed invention obvious over co-pending Application No 09/615,154.

Furthermore, while the Action does not assert this ground as the basis for the rejection, pre-emptively, Applicants note that they are unaware of any law in which inherent anticipation can be employed with a reference available as prior art under 35 U.S.C. § 102(f). Unlike the present specification, the cited co-pending application does not report data regarding any effect of MDA-7 on angiogenesis. It is unclear how the inventors of the current application could have *derived* the invention from the co-pending application.

As such, Applicants respectfully request this rejection be withdrawn.

G. Claims 1, 7-9, 16-23, 36-41, 75, and 76 Are Not Obvious over Roth and Fisher

The Action rejects claims 1, 7-9, 16-23, 36-41, 75, and 76 under 35 U.S.C. § 103(a) as being unpatentable over Roth *et al.* (U.S. Patent 6,069,134) ("Roth") in view of Fisher (U.S. Patent 6,355,622). It argues, "Clearly inhibiting angiogenesis encompassing inhibiting tumor [sic], a species of a genus of diseases, which has been clearly taught by Fisher *et al.* in view of Roth *et al.*" Action at page 13 (citations omitted). It further contends that it is well established that a species of a claimed invention render the genus obvious. Applicants respectfully traverse this rejection.

Again, the Action has misread the claims. The invention is directed to a method of inhibiting angiogenesis. The cited references simply do not teach this. Moreover, no every method of treating cancer results in a method of inhibiting angiogenesis. Consequently, the issue regarding genus/species is irrelevant in this context because one is not a species of the other. The Action misunderstands that by electing inhibiting angiogenesis of an angiogenesis-dependent cancer that Applicants have elected a species of a method of treating cancer.

A proper *prima facie* case of obviousness requires that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP §2142. No evidence has been provided of this. Neither Roth nor Fisher is directed to a method of inhibiting angiogenesis. Consequently, they do not teach or suggest this claim limitation. Accordingly, a proper *prima facie* case has not been made.

Notwithstanding the absence of a proper ground for rejections, Applicants further provide evidence discussed above that that the claimed invention was surprising and unexpected. A role for MDA-7 in cancer was provided solely in the context of terminal differentiation and apoptosis. Its effect in cancer was concentrated only on cancer cells; there was no suggestion or teaching that it may have an effect on angiogenesis, much less the ability to actually *inhibit*

angiogenesis. *See* Su *et al.* and Fisher. The present rejection cites to Roth, which involves a different tumor suppressor gene. In Roth, p53 is discussed only in the context of apoptosis as well. *See e.g.,* first paragraph of Summary of Invention. Therefore, it was surprising and unexpected that MDA-7 could inhibit angiogenesis, particularly by reducing the amount of CD31 expressed—which is indicative of fewer blood vessels in tumors—and by reducing tube formation in HUVEC cells.

Moreover, it was surprising and unexpected that the human MDA-7 protein would act on the non-human cells in the *in vivo* mouse model. Neither Fisher nor Roth provides any indication that this would be the case.

Therefore, there are several grounds for the nonobviousness of the claimed invention. Applicants respectfully request this rejection be withdrawn.

H. Double Patenting Rejection Is Provisional

The Actions rejects claims 1-4, 7-25, 32, 35-43, 68-74, and 77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 91-116, 125, 154, and 159-174 of copending U.S. Patent Application 09/615,154 ('154 application). Applicants note that not all of these claims are currently pending in the '154 application. For instance, independent claim 91 was cancelled. Currently, claim 173 is the independent claim in the case and it reads:

> A method for treating a patient with cancer comprising 1) administering to the patient by intratumoral injection an effective amount of an expression construct comprising a nucleic acid sequence encoding a full-length or secreted human MDA-7 polypeptide under the control of a promoter operable in eukaryotic cells and 2) providing to the patient at least one other anticancer therapy, wherein the other anticancer therapy comprises performing surgery or administering chemotherapy, radiotherapy, immunotherapy, or gene therapy with a second therapeutic polynucleotide other than a polynucleotide encoding the MDA-7 polypeptide, wherein the cancer is non-small cell lung, small-cell lung, lung, hepatocarcinoma, retinoblastoma, astrocytoma, gum, tongue, neuroblastoma,

head, neck, pancreatic, renal, testicular, ovarian, mesothelioma, cervical, gastrointestinal, lymphoma, brain, colon, or bladder.

As discussed above, there is no basis for asserting that a method of treating a patient with cancer renders obvious a method for inhibiting angiogenesis. A method of inhibiting angiogenesis is not a species of a method of treating cancer, even if the method of inhibiting angiogenesis is in a patient with an angiogenesis-related cancer because not all cancer treatments will achieve inhibition of angiogenesis.

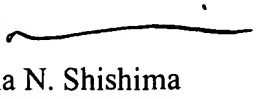
Moreover, the current claim in the '154 application recites "providing to the patient at least one other anticancer therapy." No arguments have been provided about how this claim or any of the other pending claims renders obvious *each* of claims 1-4, 7-25, 32, 35-43, 68-74, and 77. Applicants contend that there is no basis for this rejection and respectfully request it be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner wish to discuss this further, please contact the undersigned attorney at 512-536-3081.

Respectfully submitted,



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